

SYNTHETIC STRATEGIES TOWARDS A DIUREIDOCALIX[4]ARENE

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SYNTHETIC STRATEGIES TOWARDS A DIUREIDOCALIX[4]ARENE

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For my parents, Trevor and Allison Reid, my brother, Kester and my sister, Renell
with love

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TABLE OF CONTENTS

ACKNOWLEDGEMENT.....	iv
LIST OF FIGURES.....	vi
LIST OF SCHEMES	vii
LIST OF SYMBOLS AND ABBREVIATIONS.....	viii
SUMMARY	x
INTRODUCTION AND BACKGROUND.....	1
RESULTS AND DISCUSSION.....	20
EXPERIMENTAL AND SPECTRAL DATA.....	26
REFERENCES.....	36

LIST OF FIGURES

	Page
Figure 1. Calix[n]arene structure.	1
Figure 2. Calix[4]arene conformations.	3
Figure 3. Schematic Diagram of a tetra ureacalix[4]arene dimer.	6
Figure 4. Ureidocalix[4]arene heterodimers.	7
Figure 5. Ureidocalixarene derivatives of investigation by mass spectrometry.	9
Figure 6. Quaternary ammonia salts for ESI mass spectrometry.	10
Figure 7. Guests for encapsulation by expanded tetraureacalix[4]arene.	16
Figure 8. Ureidocalix[6]arenes for dimerization.	18
Figure 9. Proposed structure of diureido calix[4]arene dimer.	20
Figure 10. ¹ H- NMR of chloropropylurea-tetrapropylcalix[4]arene 32	31
Figure 11. ¹³ C- NMR of chloropropylurea-tetrapropylcalix[4]arene 32	32
Figure 12. ¹ H-NMR of Fmoc-3-(3-propylureido)propylcarbamate 38	33
Figure 13. ¹³ C-NMR of Fmoc-3-(3-propylureido)propylcarbamate 38	34
Figure 14. ¹ H- NMR of 1 -(3-Amino-propyl)3-propylurea 39	35
Figure 15. ¹³ C- NMR of 1 -(3-Amino-propyl)3-propylurea 39	36

LIST OF SCHEMES

Scheme 1. Synthesis of Calix[n]arenes.	2
Scheme 2. Synthesis of phenylureacalix[4]arene.	6
Scheme 3. Synthesis of Ureidopeptide calix[4]arene.	12
Scheme 4. Calixarene for investigation of ureido calixarene chirality.	13
Scheme 5. Synthesis of expanded tetraurea calix[4]arene.	15
Scheme 6. Synthesis of Ureidopyrimidinonoyl calix[4]arene dimer.	17
Scheme 7. Synthesis of tetraaminocalix[4]arene	21
Scheme 8. Towards synthesis of diureidocalix[4]arene 1.	22
Scheme 9. Towards synthesis of diureidocalix[4]arene 2.	23
Scheme 10. Towards synthesis of diureidocalix[4]arene 3.	24
Scheme 11. Towards synthesis of diureidocalix[4]arene 4.	25

LIST OF SYMBOLS AND ABBREVIATIONS

Å	angstroms
amu	atomic mass units
°C	degrees Centigrade
CD	circular dichroism
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EtOAc	ethyl acetate
ESI	electron spray ionization
Fmoc	fluorenylmethoxycarbonyl
FRET	Fluorescence Resonance Energy Transfer
g	gram
h	hour
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Hz	hertz
K_a	association constant
KOH	potassium hydroxide
LDA	lithium diisopropylamide
Leu	Leucine

M	molar concentration
MeOH	methanol
mg	milligram
mL	milliliter
mM	millimolar
mmol	millimole
mol	mole
NaHMDS	sodium bis(trimethylsilyl)amid
Nm	nanometer
NMR	Nuclear Magnetic Resonance
Ph	phenyl
pH	hydrogen ion concentration
ppm	parts per million
R	unspecified alkyl group
ROESY	Rotational nuclear Overhauser Effect Spectroscopy
RNA	ribonucleic acid
r.t.	room temperature
s	seconds

SUMMARY

Self-organization in molecular assembly is a common concept among molecules in nature. Some examples of this process include the ability of a protein to find its stable tertiary structure and the coming together of two flexible strands to form a DNA double helix. Therefore, investigations into how and why these molecules come together by intermolecular forces have captured the interest of scientists. Synthetic molecules able to mimic nature's self-organization have become important in the area of supramolecular chemistry. These studies are intended to bring us closer towards nature-like assemblies. Calixarenes belong to group of bowl-shaped molecules investigated for their ability to self-assemble into dimeric capsules. The cavities formed within these capsules can reversibly bind guest molecules and can be useful for catalysis, molecular recognition and for encapsulation of drug molecules. Efficient and uncomplicated synthesis and functionalization of calixarenes makes them appealing targets for this type of chemistry.

Experimental approaches towards the synthesis of a diureidocalix[4]arene are described, in which tetrapropylcalix[4]arene is substituted on the upper rim with urea groups that are separated by a hydrocarbon spacer. This molecule will be used to investigate the dimerization properties of such as structure. The majority of investigations of ureido calix[4]arenes previously investigated only explored dimerization through one set of hydrogen bonds. However, it is projected that this new molecule will provide increased stability and stronger binding through hydrophobic interaction of the hydrocarbon chain as well as an additional set of hydrogen bonds.

CHAPTER I INTRODUCTION AND BACKGROUND

Calix[n]arenes

Calixarenes are macrocyclic compounds composed of phenol units joined together by methylene spacers (**Figure 1**). They are the single-step product of a condensation reaction of *para*-substituted phenol and formaldehyde under alkaline conditions (**Scheme 1**).

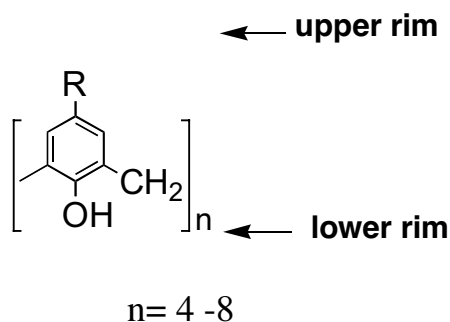
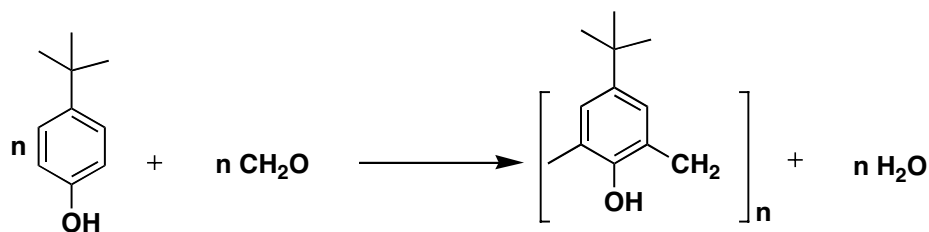


Figure 1. Calix[n]arene

The reaction conditions employed determine the ring size of the calixarene that is formed. The most common of these rings are the even numbered calix[4], calix[6] and calix[8]arene, which are efficiently synthesized in yields of 50%¹, 85%² and 63%³ respectively. Calix[4]arenes and calix[8]arenes can be synthesized with approximately 0.03 moles NaOH per mole of *tert*-butylphenol but calix[4]arenes require much higher temperatures. In contrast, larger amounts of base are required to favor the formation of calix[6]arene (0.4 moles of KOH per mole of *tert*-butylphenol).



Scheme 1. Synthesis of Calix[n]arene

Calix[5]arene can be synthesized in fairly satisfactory results in 15-20% yield⁴ and more recently there has also been a report of the synthesis of calix[7]arene in 11-17% yield.⁵

Although *tert*-butylphenol is currently the starting material of choice for synthesis of calixarenes, there are other *para*-substituted phenols that have been used, but often with less clean results. For example, *para*-benzylphenol has been reported to give *para*-benzylcalix[6]arene in 33% yield along with some *para*-benzylcalix[8]arene⁶. Other phenols can be used to give *para*-methylcalix[6]arene in 74% yield;⁷ *para*-adamantylcali[8]arene in 72% yield,⁸ and *para*-benzyloxycalix[8]arene in 48% yield.⁹

Calix[4]arenes are by far the most commonly studied calixarenes and are widely studied for their use in supramolecular chemistry for self-assembly, recognition, sensing and encapsulation. Calix[4]arenes can exist in one of four stable conformations, which are known as *cone*, *partial cone*, *1,2-alternate* and *1,3-alternate* (**Figure 2**). Calix[4]arenes prefer the cone conformation, which is stabilized by intramolecular hydrogen bonding of the hydroxyl groups on the lower rim.

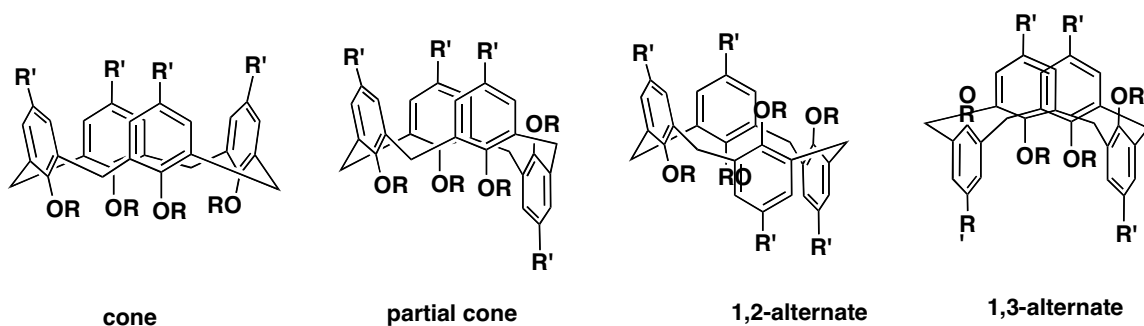


Figure 2. Calix[4]arene conformations.

Calix[4]arenes are an excellent choice for supramolecular chemistry, especially since modifications can be easily made to the lower (narrow) and upper (wider) rim.

Modifications of the lower rim

O-alkylations and O-acylations can be readily achieved on these molecules. This synthesis is of vital importance because the molecules can be fixed into a particular calix[4]arene conformation by alkylation of the lower rim with large substituents. It has been shown that alkylation of the phenolic oxygens with propyl (or larger) groups can inhibit “oxygen through the annulus” ring inversion, thus locking the rings into a particular conformation. Tetraalkylation of calix[4]arene is generally achieved using an excess of alkylating agent in the presence of a strong base such as NaH.¹⁰ The formation of tetraalkylated derivatives solely in the cone conformation can be favored by the presence of metal ions such as Na⁺. For example, in the reaction of *tert*-butyl calix[4]arenes with ethylbromoacetate in the presence of Na₂CO₃ or NaH affords 100% of the *cone* conformer, while the 1,3 *alternate* conformation is obtained the presence of Cs₂CO₃.¹¹

Selective O- alkylation and O- acylation of calix[4]arenes is also possible, where one, two or three of the phenolic OH groups can be alkylated. Monoalkylated tertbutylcalix[4]arene can be synthesized by using an alkylating agent with NaH in toluene,¹² Ba(OH)₂ as a base in DMF¹² or 1.2 equivalents of a weak base such as K₂CO₃ in MeCN.¹³ Dialkylations of the 1,3 type can be synthesized in high yields by using an excess of an alkylating agent using similar conditions as for the monoalkylation product. For example, *t*-butylcalix[4]arene treated with excess benzylbromide in acetone, with K₂CO₃ as a base gave 1,3 dibenzyl ether.¹² 1,2-diethers are also possible using a strong base with a limiting amount of alkylating agent, and trimethylation of calix[4]arene is readily achieved using Me₂SO₄ in DMF in the presence of BaO.Ba(OH)₂.¹⁴

Modifications of the upper rim

Modification of the upper rim of calix[4]arenes involves substitution at the position *para* to the phenolic oxygen. The *tert*-butyl group can be removed by an AlCl₃-catalyzed reaction in the presence of an acceptor such as phenol or toluene.¹⁵ After removal of the *tert*-butyl group electrophilic substitutions can be added to the *para*-position. Substitution at this position includes halogenation,^{16, 17} nitration,¹⁸ sulfonation,¹⁹ sulfochlorination,²⁰ acylation,²¹ chloromethylation²² and aminomethylation^{23, 24}. Nitration²⁵ and sulfonation²⁶ by ipso-substitution of the *tert*-butyl groups can also be obtained. Once these substituents have been introduced they can undergo further reactions such as reduction of the nitro groups²⁷ and acyl groups,²¹ further substitution at chromethyl groups and aryl-aryl Suzuki coupling,²⁸ to name a few examples.

If substitution on at all four positions is not desired, selectivity can be achieved by first functionalizing the hydroxyl groups on the lower rim as described in the previous section. As a rule, ether and ester groups are less reactive than their corresponding phenol groups and as a result, the selectivity can be achieved at *para*-position on the upper rim.^{25, 27}

Ureidocalixarene Capsules

In the forefront of molecular capsule research are concave shaped structures such as clefts,²⁹ armatures,³⁰ tweezers^{31, 32} and bowl shaped molecules³³. These are advantageous because they provide an easily modified surface to recognize an external molecule. Calix[4]arene molecules fixed into a cone or bowl shape have been shown to be excellent candidates for capsule formation and several examples are available of calixarenes functionalized on the upper rim with urea moieties that dimerize into molecular capsules with a well-defined cavity.

In an appropriate solvent, two urea calix[4]arene monomers organize into a seam of hydrogen bonds around the equator of the capsule. The first of these dimers described is a calix[4]arene designed to reversibly dimerize with 16 hydrogen bonds.³⁴ This was accomplished on tetra benzyl calix[4]arene modified on the upper rim with phenyl urea moieties. A dimer was formed by a cyclic array of 8 ureas, hydrogen bonding in a "head to tail" fashion (**Figure 3**).

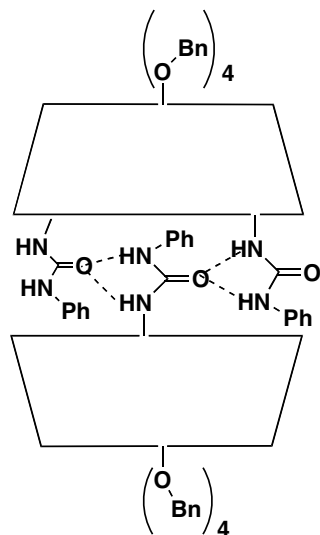
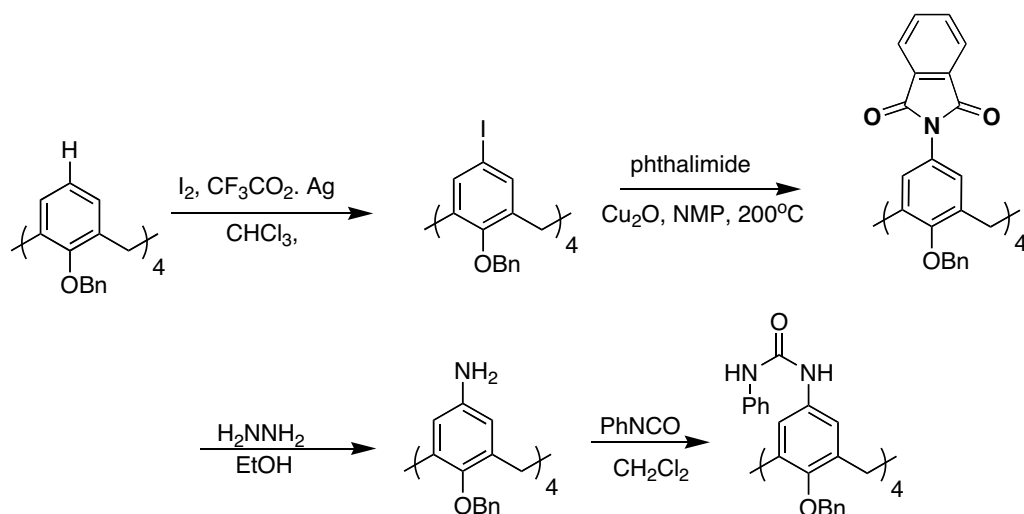


Figure 3. Schematic diagram of Tetraureacalix[4]arenes dimer **1.1**

Rebek synthesized this molecule in four steps (**Scheme 2**). Calix[4]arene undergoes iodination, then Ulmann coupling and hydrazinolysis to introduce four *p*-amino groups to the upper rim. The amino calix[4]arene is subsequently treated with phenyl isocyanate to give the desired tetraurea in 67% overall yield.



Scheme 2. Synthesis of tetraureacalix[4]arene **1**.

^1H -NMR spectroscopy and solvent encapsulation provided evidence for dimer formation. The NMR spectra of the dimer in non-polar solvents such as CDCl_3 showed asymmetry in contrast to competitive solvents such as DMSO, which disrupts the hydrogen bonding. Most importantly, the signal for the aromatic protons of the calixarene splits into 2 *meta* coupled doublets and there is also a large separation of singlets for NH-protons. It was proposed that the circular hydrogen-bond arrangement of the dimer forces all the ureas to point in the same direction, thereby slowing the rotation about the aryl-urea bond.

The best evidence for dimer formation was provided by the encapsulation of solvent molecules within the dimer cavity. For example, gradual addition of benzene- d_6 to a solution of the dimer in toluene- d_8 , led to the appearance of a second calixarene species. The two calixarene species was attributed to be dimers containing toluene- d_8 and benzene- d_6 respectively. Therefore, addition of more benzene- d_6 shifted the equilibrium further to the benzene containing species. Through such experiments, chloroform, benzene and toluene were shown to be the good guests, while ethyl benzene, p-xylene and o-xylene were not.

Besides these homodimers, there has been the synthesis of mixed heterodimers formed in apolar solvents by calix[4]arenes consisting of two different urea derivatives (**Figure 4**).³⁵ Two calixarenes with two different urea derivatives **a** and **b** can form dimers **aa** and **bb** in an apolar solvent. However, a mixture of **a** and **b** will also contain a mixed heterodimer **ab**. As for the homodimers, evidence for dimer formation was provided ^1H -NMR data and X-ray diffraction of these dimers containing a benzene guest.

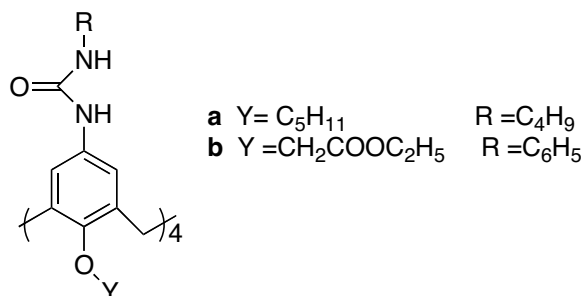


Figure 4. Ureidocalix[4]arene heterodimers.

Additional evidence for the formation of dimers of ureidocalix[4]arenes has been provided by mass spectrometry.³⁶ These studies were meant to provide independent evidence of encapsulation complexes outside those already provided by NMR experiments. In these studies, several urea calix[4]arene derivatives (**Figure 5**) were investigated using electrospray ionization (ESI) techniques. These derivatives included three calix[4]arene monomers (**2-4**) each with different side chains, one structure in which two ureidocalix[4]arenes has a flexible bridge at their upper rim (**5**), another

calix[4]arene pair that has a very rigid bridge between the lower rims (**6**) and a trimer (**7**) that was used to investigate larger aggregates by this method.

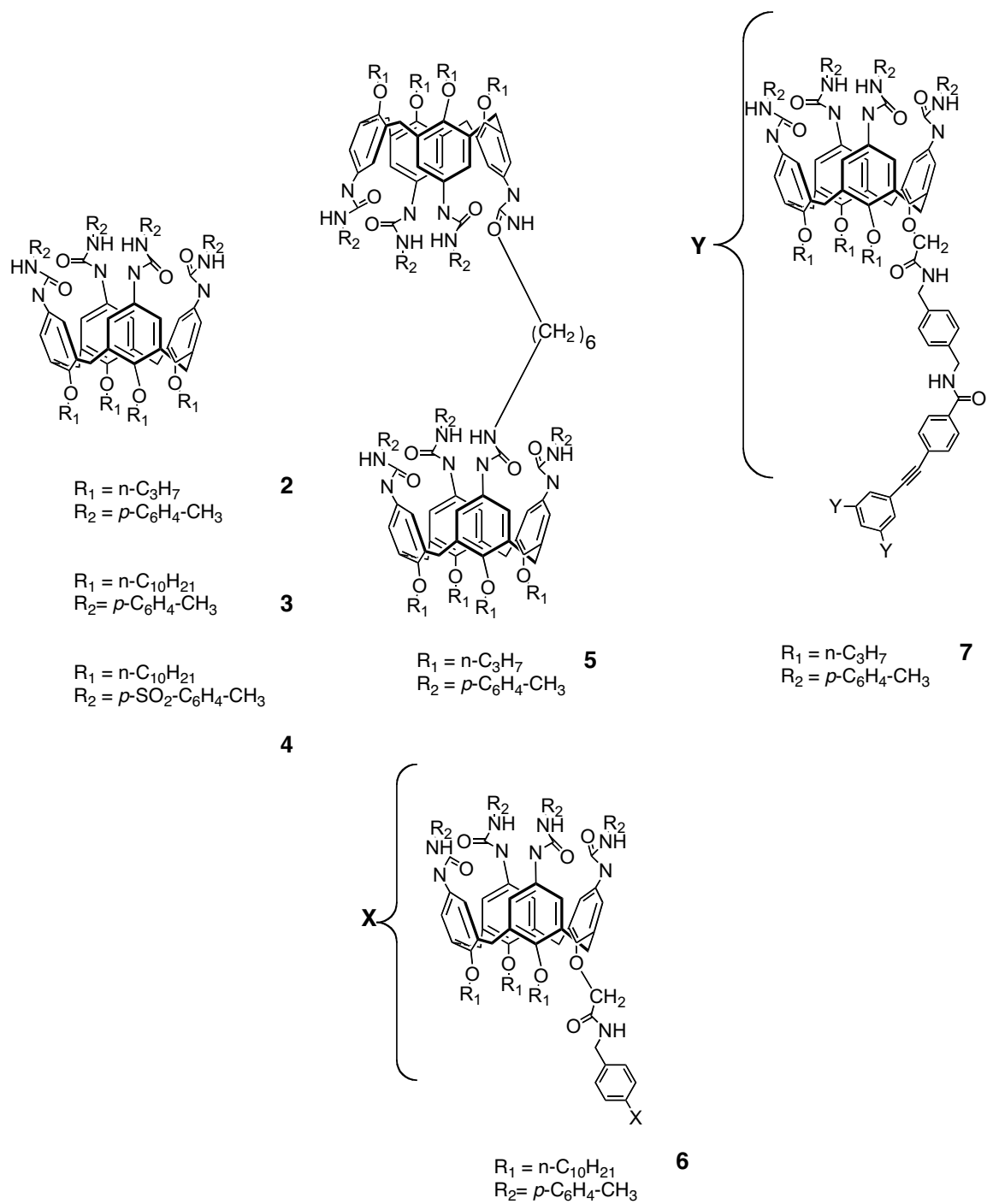


Figure 5. Ureidocalixarene derivatives for investigation by mass spectrometry

Since it was already well known that quaternary ammonium ions bind to calixarenes by cation- π bonding,^{37, 38} they were chosen to provide the charge necessary for mass spectrometric analysis. Several of these quaternary ammonium salts of different sizes and shapes were used in their investigation (**Figure 6**).

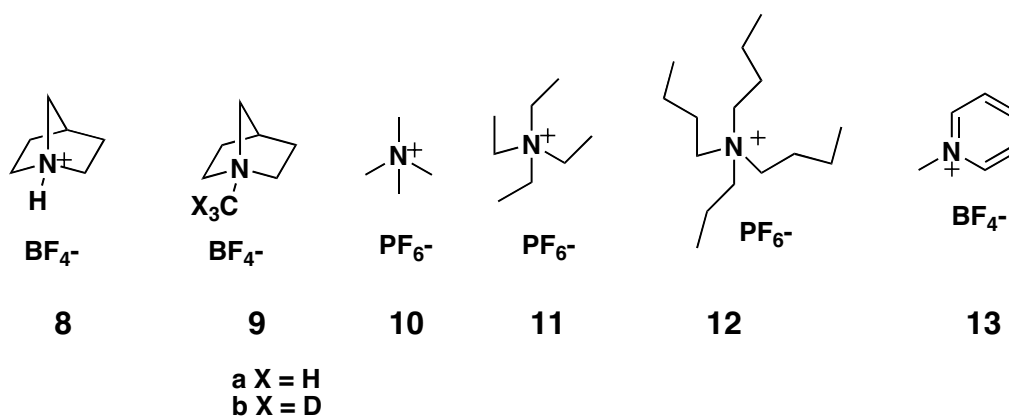


Figure 6. Quaternary ammonium salts for ESI mass spectrometry

The authors found that the ESI mass-spectra of calixarene **2** with **9**, **11** and **13** as guests showed expected m/z values at 2495 for **9a** in capsule **2.2** [**9a@2.2**], 2499 for [**11@2.2**] and 2463 for [**13@2.2**]. Replacement of **9a** with isotopically labeled **9b** caused a mass shift of

$\Delta m = 3$ amu confirming the presence of one cation and two calixarene monomers. In addition, the introduction of 10% methanol as a competitive solvent led to the complete removal of the signal for [**9a@2.2**] and the only base peak corresponded to the protonated capsule monomer [**2.H**⁺]. This method also proved valuable for the investigation of heterodimers **3.4** and **2.4**, which also showed the appropriate m/z values for these complexes with ion **9a**. Larger aggregates such as the bridged dimer of **4** were

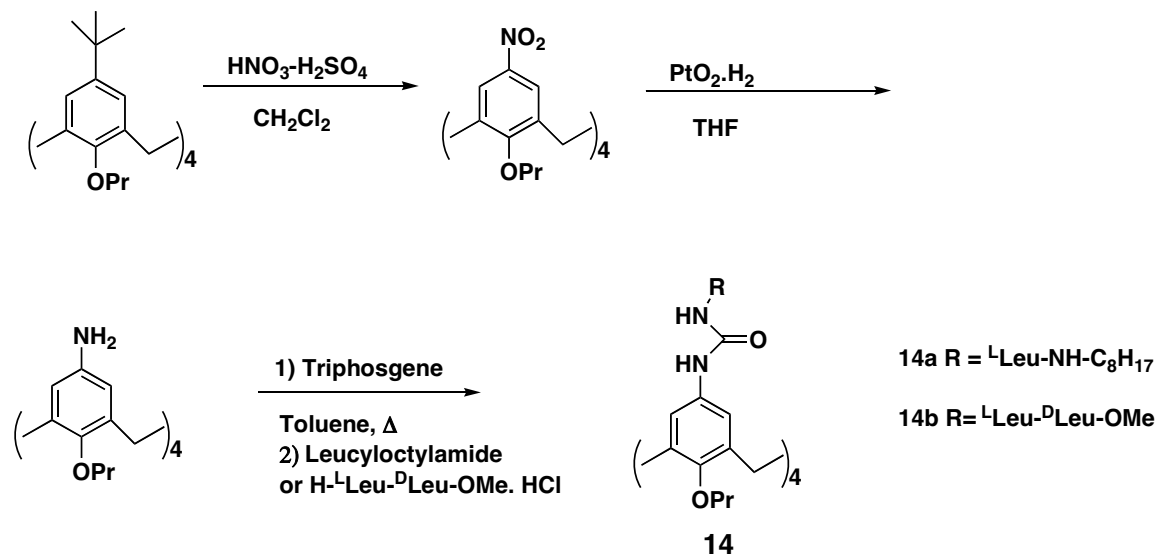
also investigated. In this case, ESI was used to distinguish intramolecular capsule formation for **[9a@4]** from intermolecular cyclic oligomers **[9a@4]_n** where $n \geq 2$. It is difficult to distinguish the two by NMR however isotopic analysis by MS was very useful because the **[9a@4]** had an isotopic peak pattern of $\Delta m=1$ and that of **[9a@5]_n** had $\Delta m=1/n$. The ESI spectra for guest **9a** with larger aggregates **6** and **7** also showed expected m/z values. This ESI method was complementary to the results found by NMR and the detection of heterodimers by this method was easier as well.

As previously mentioned, calix[4]arenes can occupy four possible conformations, and fixing the calixarene in the cone conformation is usually achieved by O-alkylation at the lower rim with groups of propyl or larger. There has been evidence that calixarenes in partial cone conformation can be forced into the cone conformation through dimerization by ureas hydrogen bonding on the upper rim as a kind of template effect.³⁹ Calix[4]arene substituted on the lower rim with methoxy groups is flexible enough to display all four conformations. Tetramethoxy calix[4]arene was substituted on the upper rim with ureas following the same synthetic procedures described before.³⁹ ¹H-NMR of the tetraamino calix[4]arene indicated that it was 96% partial cone and 4% cone. However, NMR results show that the tetraurea dimer was in 100% cone conformation. It was thus demonstrated that the hydrogen bonding of the ureas on the upper rim of calix[4]arenes could provide a well-defined cavity from an initially flexible molecule.

This template effect is further demonstrated in NMR experiments of a lower symmetry urea calix[4]arenes.⁴⁰ The presence of the methoxy group on the lower rim can pass through the ring causing the calixarene to assume a partial cone or 1,3 alternate

conformation. Even though the *tetra*-nitro derivatives did show 91% partial cone and 9% cone, the dimer of this calixarene was totally in the cone conformation.

Dimerization of ureidopeptide calix[4]arenes has also been achieved.⁴¹ The peptides chains attached to the ureas were expected to provide additional hydrogen bonding.

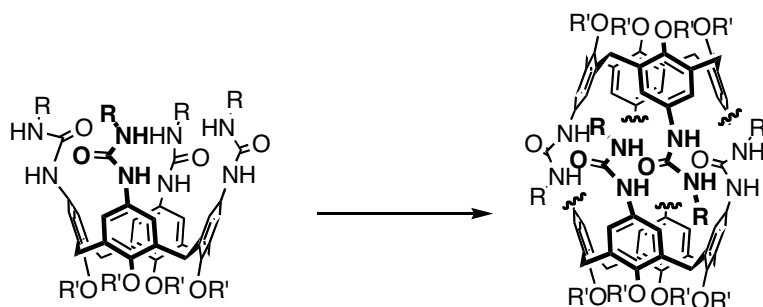


Scheme 3. Synthesis of Ureidopeptide Calix[4]arene

Calix[4]arenes substituted on the upper rim with $\text{-NHCONH}^1\text{LeuNHC}_8\text{H}_{17}$ (**14a**) and $\text{-NHCONH}^1\text{Leu}^{\text{D}}\text{Leu-Ome}$ (**14b**) were employed to mimic the scaffolds found in the α -helices or antiparrallel β -strands of secondary protein structure.⁴¹ Dimer formation by these compounds were examined using $^1\text{H-NMR}$ and ROESY data. The dileucyl compound **14b** has been shown to self-assemble through urea-urea hydrogen bonds, in addition to the set of hydrogen bonds due to the peptide side chains. On the other hand, the tetramide **14a** was a monomer under all experimental conditions. This was attributed

to the steric hindrance of the octyl side chains of the substituents linked to the ureas.

Other examples of tetraureacalix[4]arenes with amino acids showed very interesting properties. A ureacalix[4]arene dimer arranged in its common head-to-tail arrangement could either be in a counterclockwise (CCW) or clockwise (CW) direction, such that they are enantiomers. However, equal amounts of CW and CCW species exist so there are no energetic differences between them. The presence of amino acids on the urea functions has been shown to have a dramatic effect on the dimerization behavior. The chiral urea derivatives tend to assemble with aryl urea calix[4]arenes over themselves and heterodimerization was shown to occur exclusively with amino acids with β -branched side chains such as isoleucine and valine. Also the chirality of the amino acids is transferred to the capsule leading to only one direction of the urea head-to-tail arrangement. In addition, chiral guests recognize the chirality of the capsule. This phenomenon was initially observed when a capsule formed with arylureacalix[4]arene (**15**) and an amino acid derivative (**16a**) was able to bind (+)-nopinone in a preferred orientation.⁴² The diastereomer, dimer **15.16b** showed an opposite sense of urea directionality. The binding of the (+)-nopinone with the **14.15a** system and the binding of (-)-nopinone with the **15.16b** system were identical. This discovery was significant since it showed that the stereochemistry of the lining of the interior of the capsule is controlled by the chirality of the amino acid substituents.



- 15:** R = C₆H₄-*p*-C₇H₁₅, R' = C₁₀H₂₁
16a: R = *R*-norleucine-OMe, R' = C₁₀H₂₁
b: R = *S*-norleucine-OMe, R' = C₁₀H₂₁
17: R = Ile-OMe, R' = C₁₀H₂₁
18: R = Val-OMe, R' = C₁₀H₂₁

Figure 7. Ureidocalixarenes with chiral properties.

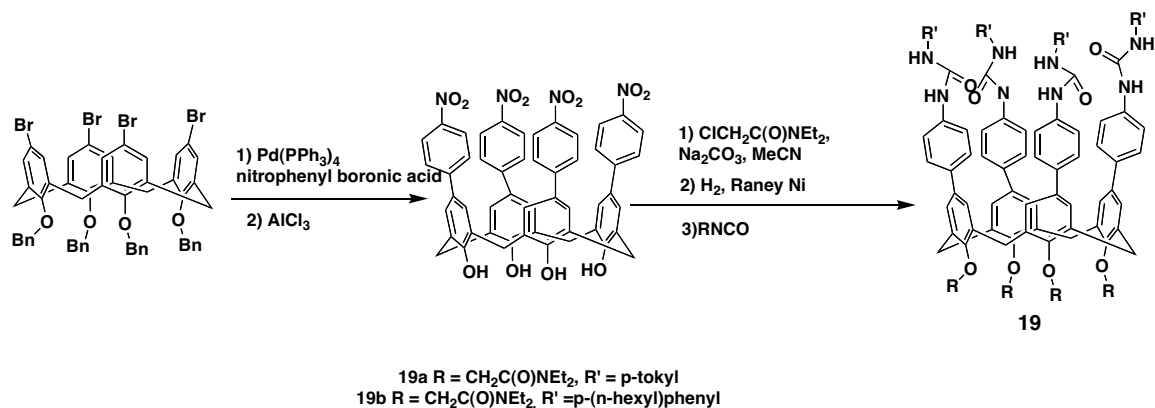
Further investigation of this remote control of capsule chirality has been explored. Calixarene derivatives with β -branched amino acids such as isoleucine (**17**) or valine (**18**) exclusively form heterodimers with arylureacalix[4]arenes in *d*-benzene instead of homodimerization with itself.⁴³ It was observed that the direction of the urea groups in these heterodimers was controlled by the chirality of the amino acid on the upper rim. The absolute stereochemistry of the **15.16** dimer was determined by circular dichroism (CD) spectroscopy and molecular modeling. Compound **16** in chloroform showed a weak CD signal, suggesting that no chirality was transferred from the amino acid to the calixarene. However, when the achiral arylureacalix[4]arene **15** was titrated into the solution of **16** large CD response was observed, which continues to increase as more of **15** was added. The authors concluded that the CD signal increase is due to coupling between the dipoles of the tolyl groups of **15** and the calixarene rings of **16**. This type of

coupling is only possible in the clockwise arrangement of the ureas as indicated by molecular modeling when viewed from the side with the arylureas. A CD curve of opposite sign and similar intensity is obtained for a heterodimer of **15** and the D-isoleucine derivative. Chiral guests within these capsule cans sense the direction of the hydrogen-bonded ureas and show selectivity in binding. For example, when R/S-norcamphor was added to a 1:1 mixture of **15** and **16**, two diastereomeric capsules were formed in the ratio of 1.3 to 1, suggesting that one of the guest enantiomers was favored. These experiments have revealed important aspects of calixarene chemistry that can be further developed to explore and understand transfer of chirality in molecular recognition events.

Although the aforementioned ureidocalix[4]arenes exhibit exciting possibilities, the cavities produced by tetraureidocalix[4]arenes are not very large as evident by the solvents that they can encapsulate, which are no larger than benzene derivatives or cubane. Substrates larger than toluene such as p-xylene are generally too large to enter the calix[4]arene capsules. Therefore, it is beneficial to pursue avenues that allow for larger capsules.

One way that was envisioned to increase capsule size was by increasing the length of tetra ureidocalix[4]arenes using phenyl spacers.⁴⁴ The synthesis of this structure began with tetra bromo tetrabenzoyloxy calix[4]arene (**Scheme 4**). The phenyl spacer was added by Suzuki reaction with p-nitophenyl boronic acid, Pd(PPh₃)₄, and Na₂CO₃ in a toluene/water solvent system. The protective benzyl group was then removed with AlCl₃ to afford tetranitrocalix[4]arene in 61% overall yield. The phenols on the lower rims

were alkylated, followed by reduction of the nitro groups to amino groups. Finally, reaction of the amino groups with the appropriate isocyanates gave the desired products.



Scheme 4. Synthesis of expanded tetraurea calix[4]arene.

In apolar solution, the product **19a** and **19b** self-assembled into dimers with a dimerization constant of $> 10^5 \text{ M}^{-1}$. This expanded tetraurea calix[4]arene dimers showed fast exchange of guests on the NMR time scale as compared to the non-expanded version **1.1** that showed slow exchange. As mentioned before, dimer **1.1** shows the presence of two species when in a solution of two deuterated solvents, while that of **19** shows only one species. This phenomenon is attributed to the large holes in the skeleton of dimer **19** that allows solvent molecules to pass in and out of the dimer at a rapid rate. Molecular modeling studies of these dimers suggested that these expanded dimers with an estimated volume of 400 \AA^3 should accommodate two benzene-sized or chloroform-sized guests.

Attempts to encapsulate neutral guests such as **20**, **21** and **22** failed, but guests **23-27** were bound to the guests due to strong ion-dipole interactions (**Figure 5**). Guest encapsulation was confirmed by ESI-MS.

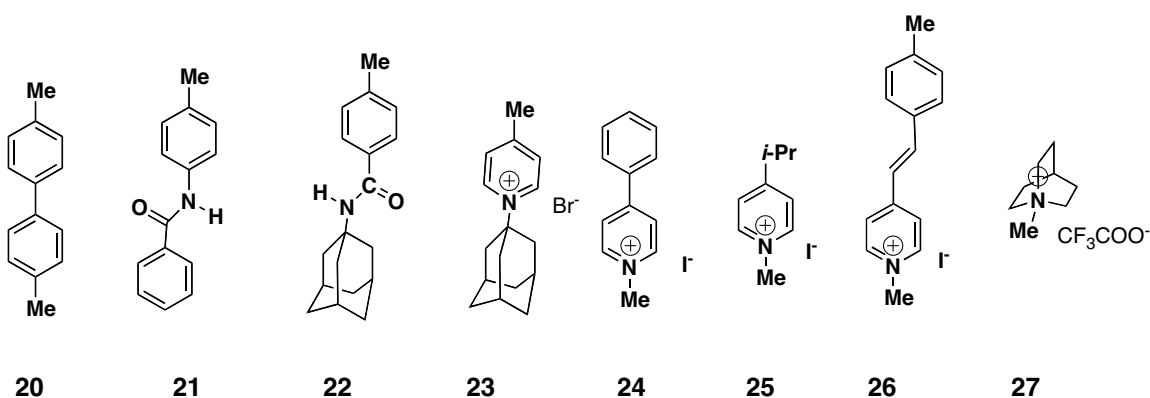
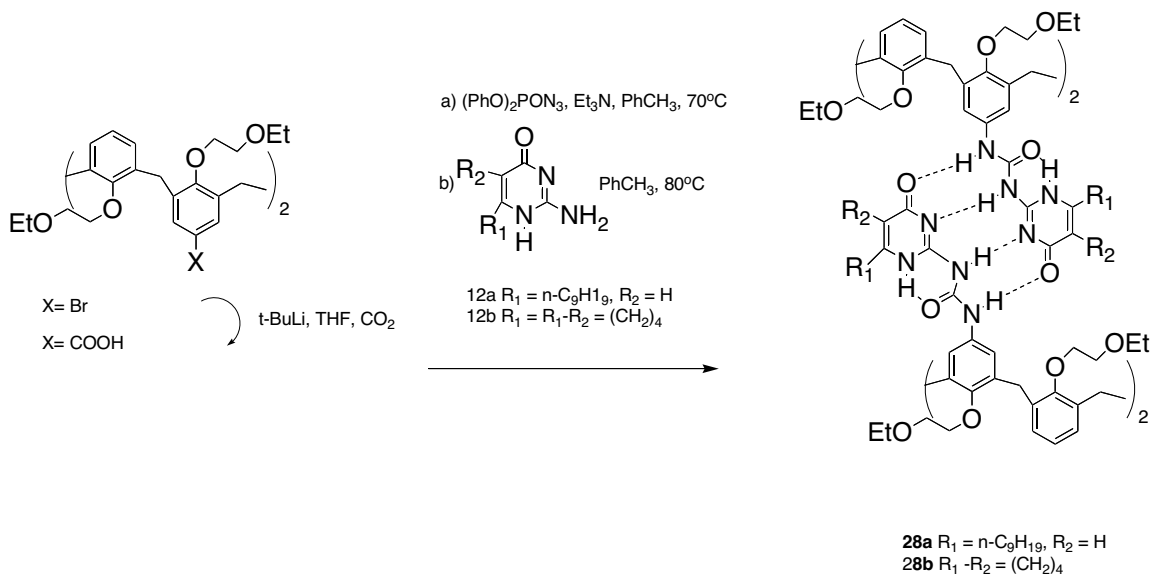


Figure 7. Guests for encapsulation by expanded tetraureacalix[4]arene.

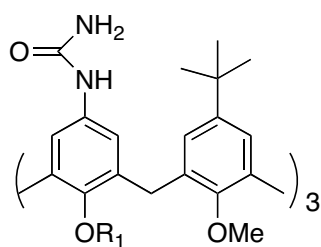
Again, in order to accommodate larger guests, researchers sought to provide a more vigorous network of hydrogen bonds to assure the self-assembly of a stable, cavity containing host. In order to achieve this, calix[4]arenes in 1,3 alternate conformation are linked by eight hydrogen bonds between ureidopyrimidinoyl groups.⁴⁵



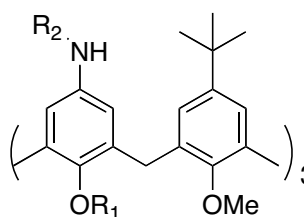
Scheme 6. Synthesis of Ureidopyrimidinonoyl Calix[4]arene Dimer.

Synthesis begins with 1,3 alternate calix[4]arene dibromide that is transformed to dicarboxylic acid by bromine/lithium exchange. The dicarboxylic compound undergoes a Curtius rearrangement with diphenylphosphoryl azide (DPPA) and the resulting bisisocyanate is reacted in situ with the appropriate 2-amino pyrimidinone to yield ureidopyrimidinonyl calix[4]arene in 78% overall yield. The dimers **28a** and **28b** produced by the ureidopyrimidinonyl calix[4]arene had a strong association constant (K_{ass}) of $> 10^6 \text{ M}^{-1}$. The ^1H NMR spectrum was used to confirm the formation of dimers showing two independent signals for the protons of the substituted arene rings. These results are similar to those obtained for calix[4]arene tetraurea dimers.

To continue the quest for increased cavity size, de Mendoza and others employed the properties of the larger calix[6]arenes.⁴⁶ The synthesis and encapsulation studies of 1,3,5 triureido calix[6]arenes were presented. The N-unsubstituted ureas **29** were prepared by reaction of amino calix[6]arenes with triphosgene or phosgene followed by treatment of the resulting isocyanate with ammonia. The N-substituted ureas **30** were obtained by reaction of amino calix[6]arenes with the appropriate isocyanate in CH_2Cl_2 as seen in previous examples.



29 a $\text{R}_1 = n\text{-C}_8\text{H}_{17}$
29 b $\text{R}_1 = \text{CH}_2\text{CH}_2\text{OEt}$
29 c $\text{R}_1 = \text{CH}_2\text{CONEt}_2$



30 a $\text{R}_1 = n\text{-C}_8\text{H}_{17}$, $\text{R}_2 = \text{CONHPh}$
30 b $\text{R}_1 = \text{Ac}$, $\text{R}_2 = \text{CONHBu}$

Figure 8 Ureidocalix[6]arenes for dimerization

^1H NMR and vapor pressure osmometry (VPO) showed that compound containing phenyl or n-butyl groups as those in **30** prevented dimerization. N-Unsubstituted 1,3,3-triureidocalix[6]arenes **29** were also monomers in polar, competitive solvents such as DMSO, however they self-assembled to form flexible dimers in less polar solvents such as benzene, toluene, CDCl_3 and CD_2Cl_2 . NMR integration also showed that there was an encapsulation of one benzene molecule per capsule. These dimers are about the same size as those arising from tetraureidocalix[4]arenes, although the shape is somewhat different.

Conclusion

Homo and heterodimers of tetraureacalix[4]arenes and their derivatives have been shown as a good choice for dimerization and encapsulation of small molecules. NMR, MS, X-ray analysis and encapsulation studies has given outstanding proof of the dimerization of these calix[4]arenes. Such molecules can be very important in molecular transport, sensing and catalysis. Although the research accomplished on these molecules have been able to enrich our understanding of these capsules, there are still many properties of these molecules that are yet to be explored. Increasing the strength and stability of these dimers through additional intermolecular forces such a hydrophobic interaction can be useful when considering containment of a host molecule. Additionally, modification of the lower rim of calixarenes with substituents that will increase water solubility is also important for use of these capsules in aqueous and biologically related environments.

CHAPTER II

RESULTS AND DISCUSSIONS

Introduction

It has already been demonstrated that ureidocalix[4]arenes can dimerize by a head to tail hydrogen bonding arrangement and that the cone shape of tetrapropyl calix[4]arenes provide a binding pocket for small molecules. The first aspect of the additional investigation of these calix[4]arenes is to enhance the strength of binding by combining intermolecular forces such as hydrophobic interactions with hydrogen bonding. The second involves modification of the lower rim with substituents that will enhance water solubility, which can have important implications in biological applications. Hence, our first goal is to design a ureidocalix[4]arene that is capable of self-assembling into a dimer by hydrophobic interactions as well as hydrogen bonding. The proposed dimer is composed of two urea moieties separated by an alkyl chain spacer attached to the upper rim (**Figure 9**).

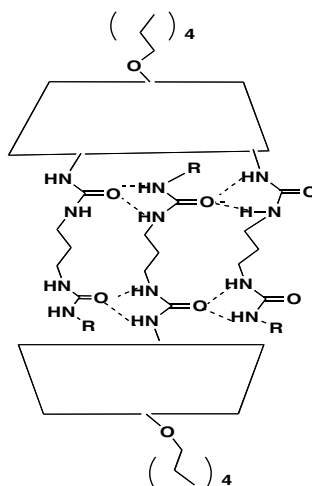
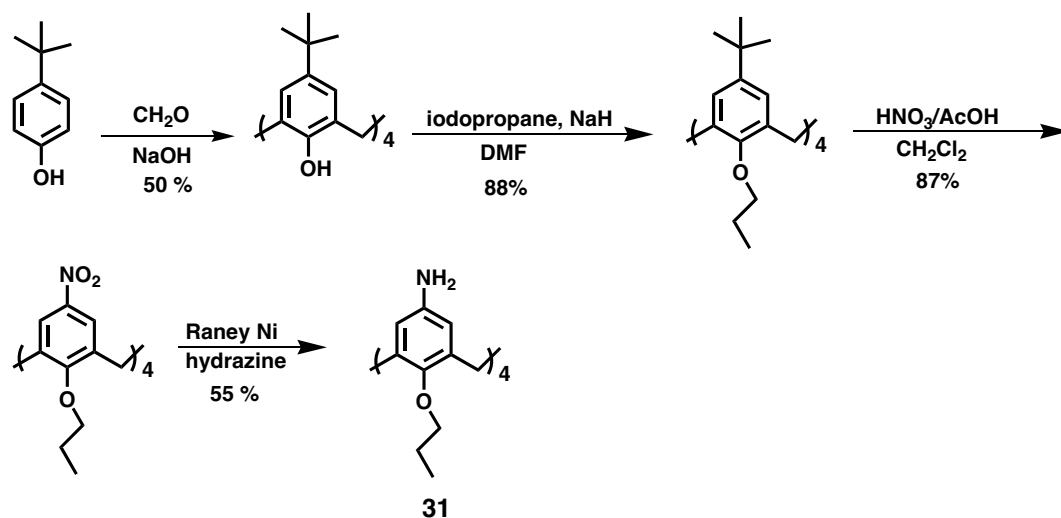


Figure 9. Proposed structure of diureido calix[4]arene dimer

A calix[4]arene modified on the lower rim with propyl groups was used since synthetic protocols on this molecule and its dimerization have already been successfully worked out. Therefore, it is an ideal molecule to test dimerization of this type before moving on to modification of the lower rim to afford water solubility. Herein, we describe the synthetic methodology involved in the design of diureidocalix[4]arene.

Preparation of tetraaminocalix[4]arene (31)

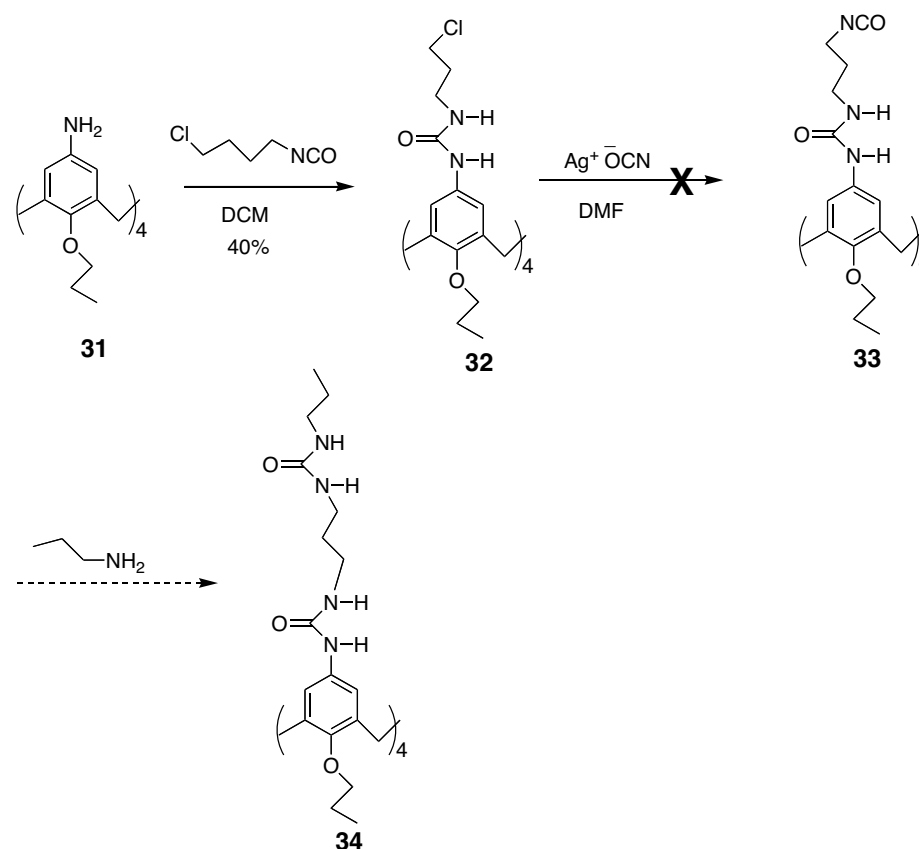
The starting material, tetraaminocalix[4]arene was first synthesized. This synthesis began with calix[4]arene, which was efficiently synthesized from tert-butylphenol and formaldehyde. Next, propylation of the hydroxyl group on the lower rim gave tetrapropylcalix[4]arene in 88% yield. Subsequent substitution of the tertbutyl group on the upper rim by ipsonitraton using nitric and acetic acid gave the tetranitrocalix[4]arene. The nitro groups of were reduced using Raney Ni and hydrazine to give the tetraaminocalix[4]arene in 55% yield.



Scheme 7

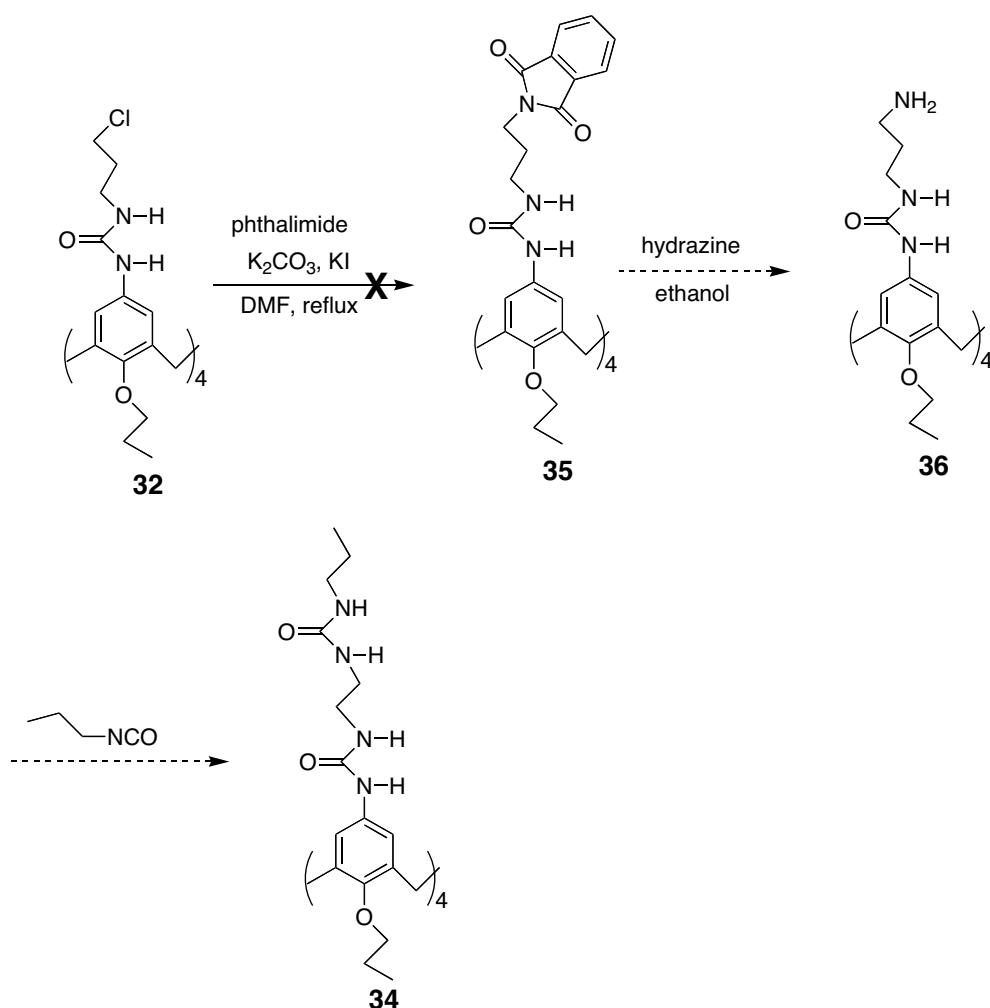
Preparation of diurea calix[4]arene

Several methods were attempted to synthesize the diurea-calix[4]arene compound. Initially, chloropropylisocyanate was added to tetraaminocalix[4]arene **31** (synthesized by literature procedures) to successfully give the tetraureachloropropyl calix[4]arene **32** (**Scheme 8**). Next, reaction of compound **32** with silver cyanate was intended to substitute the chlorine with an isocyanate group. Once compound **33** was successfully synthesized addition of propylamine would complete the synthesis of target compound **34**.



Scheme 8

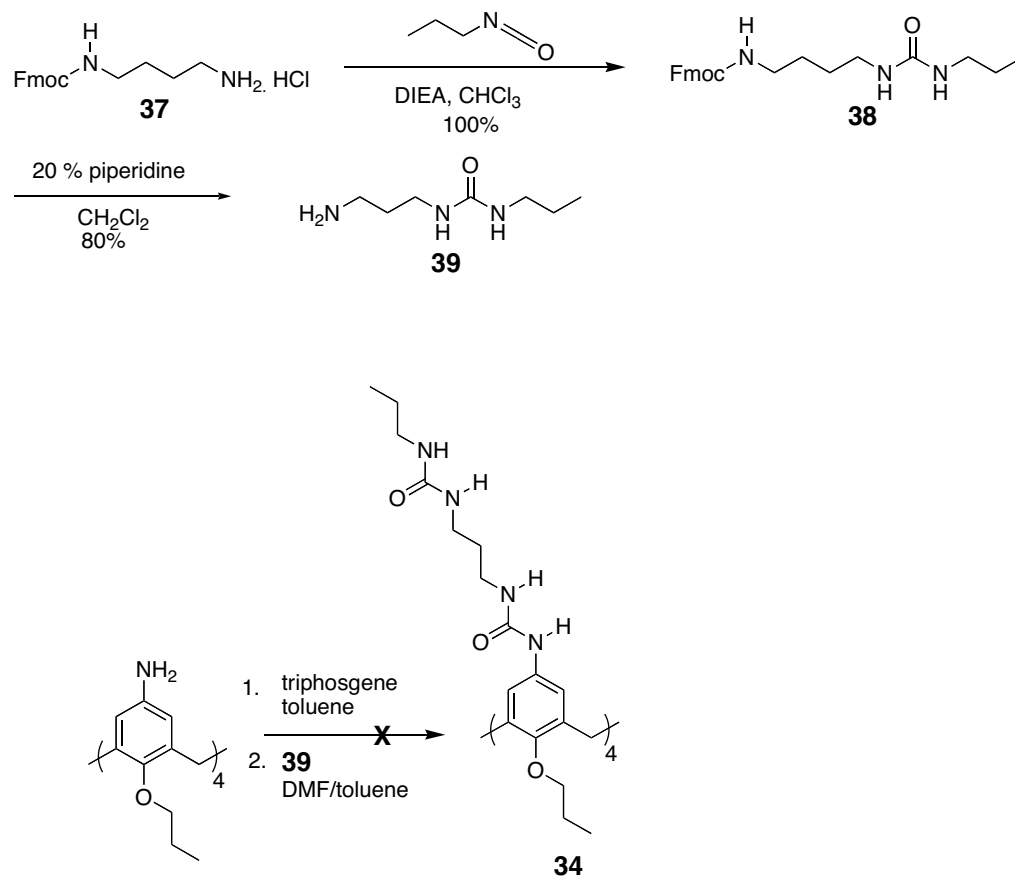
However, the reaction of **32** with silver cyanate was unsuccessful after several attempts; therefore, as an alternative, the chlorine in **32** can be substituted by phthalimide to give **35** in a Gabriel synthesis, followed by treatment with hydrazine in ethanol to obtain the amine **36**. Once product **36** was obtained, a simple addition of propyl isocyanate would have completed the synthesis of **34** (**Scheme 9**). However, the substitution reaction, may have produced some product, but in yields too low to be beneficial.



Scheme 9

Next, a four-step synthesis was envisioned to afford the synthesis of target compound **34** as shown in **Scheme 10**. First, 1-(3-aminobutyl)3-propyl-urea **38** was prepared by reaction of N-Fmoc-diaminobutane.HCl **37** with propyl isocyanate, followed by cleavage of the Fmoc protecting group with 10% piperidine in methylene chloride. Aminocalix[4]arene **31** was treated with triphosgene in toluene followed by an *in situ* addition of the resulting isocyanate with a solution of amine **39** in DMF to afford **34**.

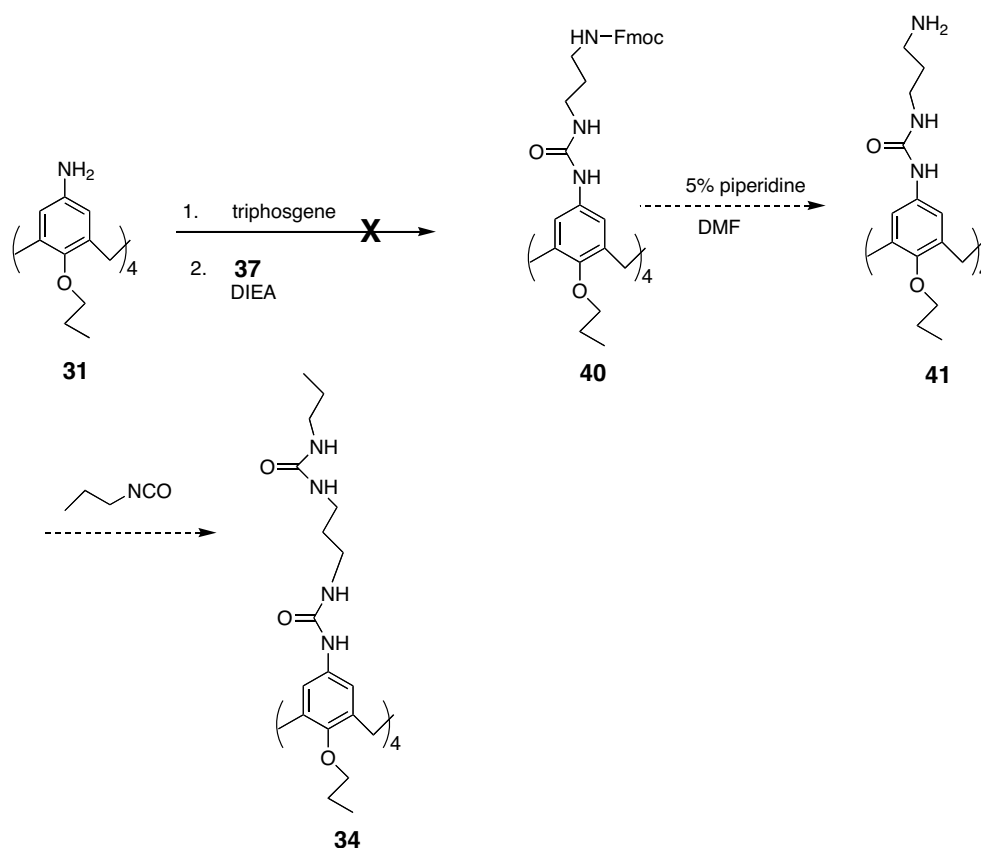
This final step to synthesize **34** was attempted several times with different solvents (toluene/DMF, DMF and DMSO) but synthesis of this product was not successful. Difficulty in this final step may have been complicated by the lack of solubility of 1-(3-aminopropyl)3-propyl-urea **39** in many common organic solvents.



Scheme 10

Finally, to overcome the lack of solubility of **39**, **scheme 11** was attempted. However, *in situ* addition of the N-Fmoc-diaminopropane.HCl to tetraisocyanate calix[4]arene failed. It was inferred that the DIEA deprotonated **37** might have been

removing its own Fmoc group, especially if the reaction of the amine with the tetraisocyanate calix[4]arene was rather slow.



Scheme 11

Several methods were utilized to synthesize the diurea calix[4]arene **34** (Schemes 7 –11). Although the final product was not obtained, several intermediates were successfully synthesized.

CHAPTER III

EXPERIMENTAL AND SPECTRAL DATA

General procedures

Reaction conditions

Oxygen- or moisture-sensitive reactions were carried out in flame-dried glassware sealed with rubber septa under a positive pressure of dry nitrogen. Air- or moisture-sensitive liquids were transferred by syringe or cannula through a rubber septa. Reaction mixtures were stirred with a Teflon covered magnetic stir bar and at room temperature unless otherwise stated.

Concentration of solutions was accomplished using a Labconco rotary evaporator with a Neuberger Laboport vacuum pump. This was followed by removal of residual solvent under high vacuum.

Reagents and solvents

Unless otherwise stated, reagents and solvents were used as received from the manufacturer without further purification, with the following exception. Dichloromethane was distilled from sodium hydride under positive pressure of argon.

Chromatography

Reactions were monitored by thin layer chromatography using 0.25 mm silica gel 60 plates impregnated with a 254 nm fluorescent indicator. Plates were visualized by UV light. Column chromatography was performed using silica gel 60, 230–400 mesh as a stationary phase.

Physical and spectral data

Melting points were recorded on a MelTemp II apparatus and are uncorrected. NMR spectra were recorded on a Varian-Gemini-400 magnetic resonance spectrometer as dilute solutions in deuteriochloroform unless otherwise stated. Proton NMR spectra are recorded in parts per million (ppm) relative to the peak of CDCl_3 (7.24 ppm), $\text{DMSO-}d_6$ (2.49 ppm), or CD_3OD (3.30 ppm). The following abbreviations apply to spin multiplicity: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), sx (sextet), m (multiplet), br (broad), and various combinations thereof. Coupling constants (J) are recorded in Hertz (Hz). Carbon-13 spectra were recorded relative to the central peak of the chloroform- d_1 triplet (77.0 ppm), the $\text{DMSO-}d_6$ septet (39.7 ppm), or the methanol- d_4 septet (49.0 ppm), and were recorded with complete hetero-decoupling. High-resolution mass spectra were recorded at the Georgia Institute of Technology mass spectrometry facility at Georgia Institute of Technology in Atlanta.

Tetraaminocalix[4]arene

A solution of nitrocalix[4]arene in MeOH was heated to 55°C, then Raney Ni and hydrazine were added. After 4 hours the reaction mixture was poured over a silica plug and the filtrate diluted with CH_2Cl_2 and washed with distilled water and brine. The organic layer was acidified with 1N HCl and the aqueous layer neutralized with saturated NaHCO_3 . The aqueous layer was then extracted with CH_2Cl_2 and the organic layer washed with brine, dried over MgSO_4 and concentrated *in vacuo*. The spectral data were in agreement with literature data.

Tetraureachloropropyl calix[4]arene (32)

To a solution of amino calix[4]arene (1.0g, 1.53 mmol) in dry methylene chloride (20 mL) was added chloropropylisocyanate (1.26 mL, 12.25 mmol). The reaction was allowed to stir at room temperature for 16 hours. The solvent was removed *in vacuo* and the product was purified by column chromatography to yield **32** (0.31g, 35%) as a light brown solid. mp = > 280°C decomposed.

¹H-NMR (DMSO-d₆): δ = 7.97 (s, 4H, NH), 6.70 (s, 8H, ArH), 5.92 (t, br, 4H, NH), 4.27 (d, J = 12.8 Hz, 4H, ArCH), 3.72 (t, J = 7.6 Hz, 8H, OCH₂), 3.62 (t, 8H, J = 6.9Hz, CH₂Cl), 3.12 (q, 8H J = 6.8 Hz, NHCH₂CH₂), 2.99 (d, J = 12.8 Hz, 4H, ArCH), 1.85 (m, 16H, CH₂CH₂), 0.94(t, J = 8.0 Hz, 12H, CH₃).

¹³C-NMR: δ = 60.7, 156.1, 139.6, 123.6, 81.9, 48.5, 41.9, 38.2, 36.2, 28.1, 15.7.

HRMS: Calc for C₅₆H₇₆N₈O₈Cl₄: 1128.4533. Found 1128.4540.

Fmoc-3-(3-propylureido)propylcarbamate (38)

To a suspension of Fmoc-diaminopropane.HCl (0.50 g, 1.33 mmol) and diisopropylethylamine (0.23 mL, 1.325 mmol) in methylene chloride (8 mL) was added propylisocyanate (0.15 mL, 1.59 mmol). The reaction was then allowed to stir at room temperature for 4 hours. The reaction mixture was then diluted with methylene chloride, washed with water, dried with MgSO₄ and concentrated *in vacuo* to give a white solid (0.53 mg, 100% yield). mp = 156.1-156.4 °C.

$^1\text{H-NMR}$ (CDCl_3): δ = 7.25 (d, J = 8.0 Hz, 2H, ArH), 7.59 (d, J = 7.2 Hz, 2H, ArH), 7.39 (t, J = 7.6 Hz, 2H, ArH), 7.30 (t, J = 7.2 Hz, 2H, ArH), 5.57 (s, 1H, NH), 5.15 (s, 1H, NH), 4.71 (s, 1H, NH), 4.36 (d, J = 6.4 Hz, 2H, OCH_2), 4.20 (t, J = 7.2 Hz, 1H, CHCH_2), 3.22–3.10 (m, 6H NHCH_2), 1.60 (qn, J = 5.6 Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.49 (sx, J = 8.0 Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_3$), 0.901 (t, J = 7.2 Hz, 3H, CH_2CH_3).

$^{13}\text{C-NMR}$ (CDCl_3): δ = 159.1, 157.3, 144.2, 141.5, 127.9, 127.3, 125.3, 120.2, 66.9, 47.5, 42.5, 37.8, 36.7, 31.0, 23.7, 11.6.

HRMS: Calc. for $\text{C}_{22}\text{H}_{28}\text{N}_3\text{O}_3$: 382.2131. Found: 382.2127.

1 -(3-Amino-propyl)3-propylurea (39)

The white solid **31** (0.45g, 1.18 mmol) was dissolved in a 10% solution of piperidine (0.8 mL, 8.09 mmol) in CH_2Cl_2 (8 mL) and the mixture was stirred at room temperature for 18 hours. The reaction mixture was filtered and the residue washed with CH_2Cl_2 and hexane to give the product as a white solid (0.15 g, 80% yield). mp = 79-82°C

$^1\text{H-NMR}$ (CD_3OD): δ = 3.20 (t, J = 6.8 Hz, 2H, $\text{NH}_2\text{CH}_2\text{CH}_2$), 3.06 (t, J = 7.2 Hz, 2H, CH_2NH), 2.80 (t, J = 6.8 Hz, 2H, NHCH_2), 1.71 (qn, J = 6.8 Hz, 2H, $\text{CH}_2\text{CH}_2\text{CH}_2$), 1.48 (sx, J = 6.8 Hz, 2H, CH_2CH_3), 0.907 (t, J = 7.6 Hz, 2H, CH_2CH_3).

$^{13}\text{C-NMR}$ (CD_3OD): δ = 158.8, 45.6, 40.1, 36.0, 34.9, 29.1, 21.7

HRMS: Calc. for $\text{C}_7\text{H}_{17}\text{N}_3\text{O}$: 159.1372. Found: 159.1363

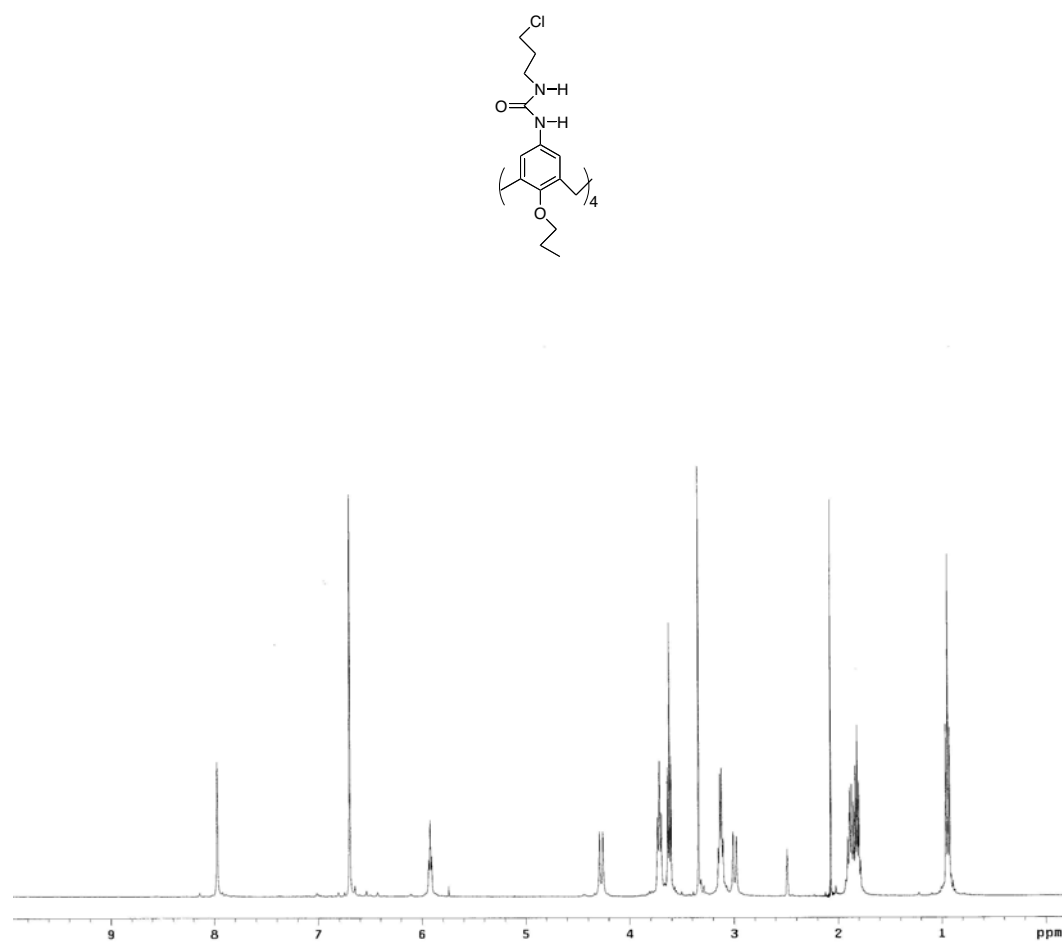


Figure 10. ¹H- NMR chloropropylurea-tetrapropylcalix[4]arene **32**

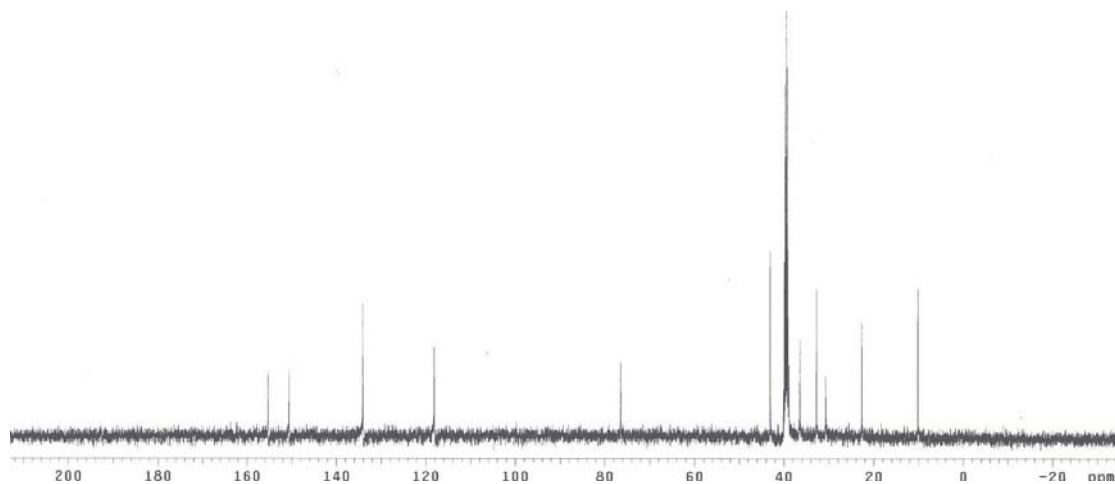
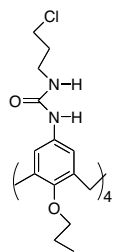


Figure 11. ^{13}C -NMR chloropropylurea-tetrapropylcalix[4]arene **32**

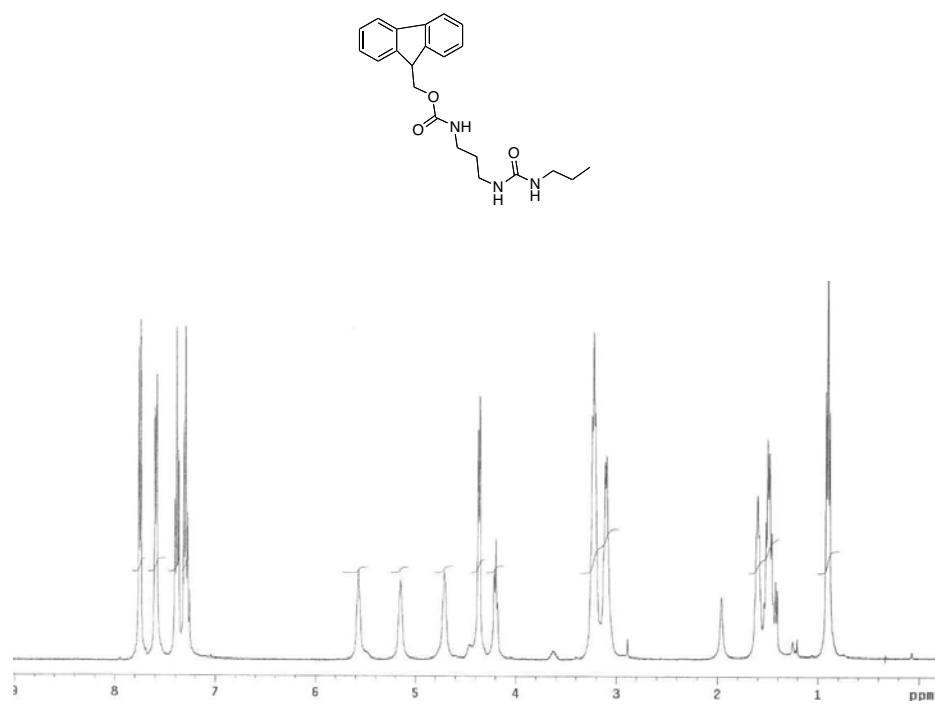


Figure 12. ¹H-NMR Fmoc-3-(3-propylureido)propylcarbamate **38**

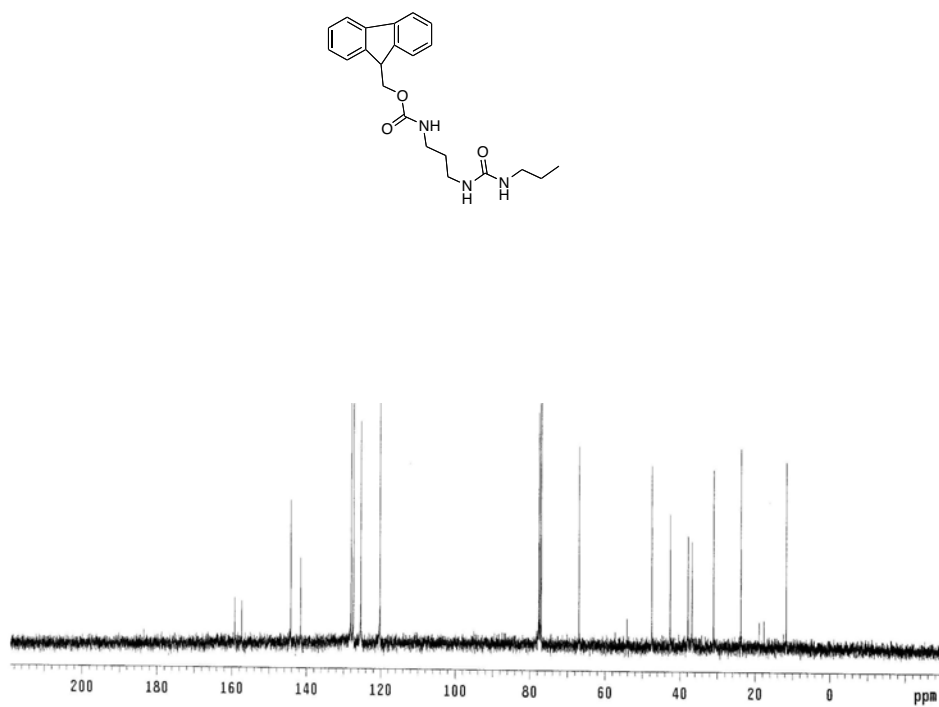


Figure 13. ^{13}C -NMR Fmoc-3-(3-propylureido)propylcarbamate **38**

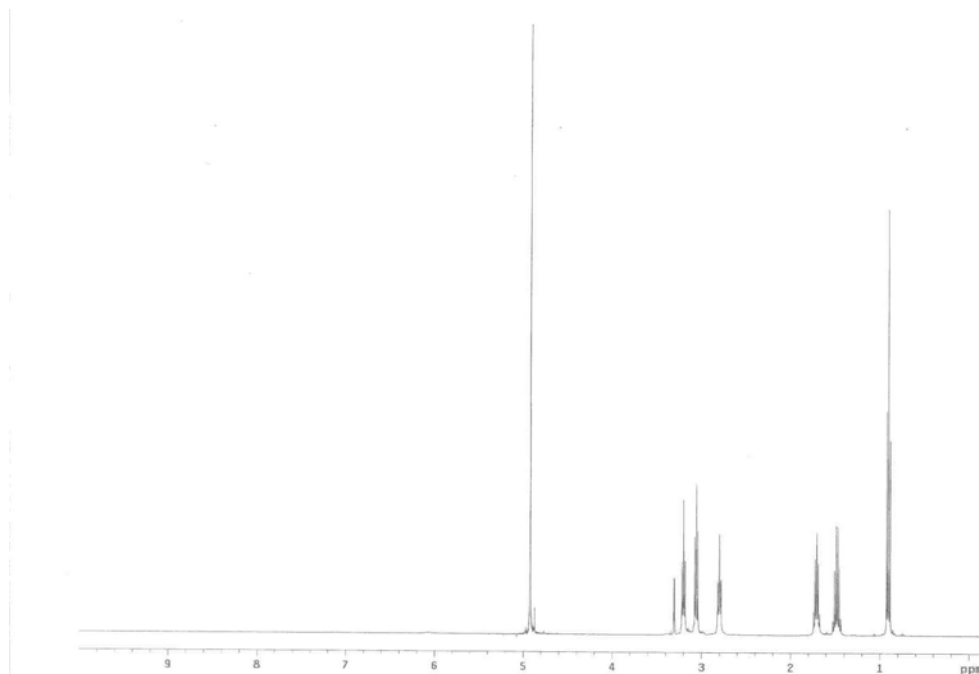
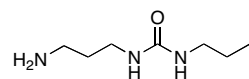


Figure 14. ^1H -NMR 1-(3-Amino-propyl)3-propylurea **39**

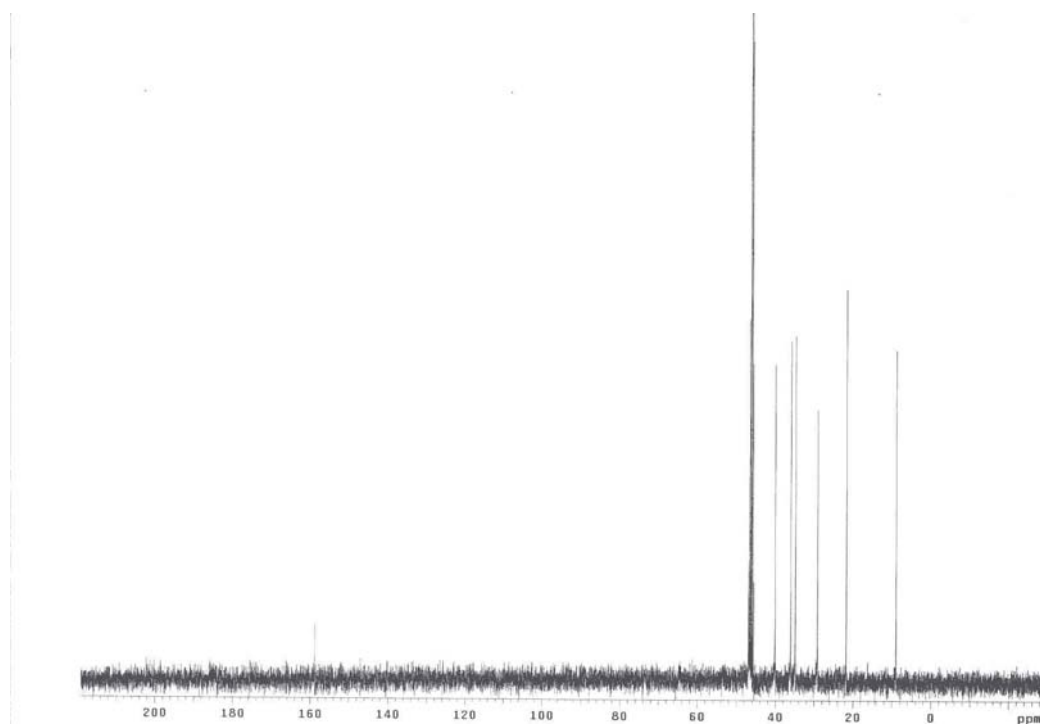
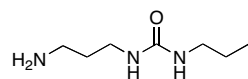


Figure 15. ^{13}C -NMR 1 -(3-Amino-propyl)3-propylurea **39**

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